IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicants: | ABBOTT, Nicholas L., et al. |
| Application No.: | 10/711,517 |
| Filing Date: | September 23, 2004 |
| Title: | USING LIQUID CRYSTALS TO DETECT AFFINITY MICROCONTACT PRINTED BIOMOLECULES |
| Atty Docket No.: | 960296.00526 |
| Examiner: | FOSTER, Christine E. |
| Group Art Unit: | 1641 |

**Pre-Appeal Brief Request for Review**

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**Request for Review**

Applicants respectfully request consideration of the following remarks in connection with a Pre-Appeal Brief Request for Review. This paper accompanies a Notice of Appeal of the final Office action of December 4, 2007 and is being submitted before the filing of an appeal brief. Applicants respectfully assert that the legal requirements have been misapplied in all of the rejections contained within the Final Office Action mailed on December 4, 2007. Accordingly, a Pre-Appeal Brief Request for Review is appropriate given the clear error and omissions made in the present case. In view of the following remarks, Applicants respectfully request the issuance of a Notice of Allowance for the pending claims 1-6, 10, 11 and 14-23.

**Standing of the Claims**

In view of the Office action mailed December 4, 2007, the claims stand as follows: claims 1-6, 10, 11 and 14-23 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite, and claims 1-6, 10-11, 15-20 and 22-23 stand rejected under 35 U.S.C. §103a as being obvious in view of Bernard et al., or alternatively over Renault et al., in view of Abbott et al. Applicants respectfully traverse these rejections and objections based on clear misapplication of the applicable legal requirements.

**Brief Summary of the Invention**

The present invention provides a method for detecting a ligand comprising (a) contacting a sample having a ligand with an affinity substrate, wherein the affinity substrate comprises a receptor capable of specifically binding said ligand, the receptor binding the ligand upon contact with the sample; (b) contacting the affinity substrate with a detection surface, wherein the ligand which is bound to the receptor is transferred to the detection surface; and (c) detecting the presence of the ligand on the detection surface by contacting the detection surface with a liquid crystal, wherein the presence of the ligand on the detection surface is detected by a change in the orientation of the liquid crystal contacted with the detection surface.

**Rejection Under 35 U.S.C. §112, Second Paragraph: Indefiniteness**

The primary purpose of 35 U.S.C. §112, second paragraph, is to ensure that the boundaries of the claims are reasonably clear and precise. Breadth of claim language is not to be equated with indefiniteness. The final Office action failed to examine the claims as required under the proper legal framework.

The Office has taken issue with the language in claim 1, step (c), "detecting the presence of the ligand on the detection surface by contacting the detection surface with liquid crystal, wherein the presence of the ligand on the detection surface is detected *by a change in the orientation of the liquid crystal* contacted with the detection surface." (Examiner's emphasis.) The Office apparently believes it is not clear what the change in orientation of the liquid crystal would be assessed relative to, since the Office believes the liquid crystal would not yet be oriented or anchored on the surface before ligand binding. Therefore, the Office finds it unclear as to how a "change in orientation" would be assessed. The Office poses the question "is the change relative to the orientation of liquid crystals on a controlled detection surface having no printed ligand? Or relative to other areas of the surface not contacted by the affinity substrate?"

Applicants respectfully submit that, when viewed in light of the specification, it is clear that the change in the orientation of the liquid crystal is in response to ligand present on the detection surface and the orientation of the liquid crystal differs upon contact with ligand relative to other areas of the detection surface where ligand is not present (see Figures 1.1 and 1.2 and paragraph [0055-0060] of the published application).

**Rejection Under 35 U.S.C. §103a**

In making a rejection under §103, the Office must articulate a reason or rationale to support that obviousness rejection. Any such reason or rationale should be based on the state of the art and not on impermissible hindsight using the Applicants' disclosure. In making an obviousness rejection, the Office may base its rationale on whether: (a) there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to the artisan to modify the references; (b) the artisan would have a reasonable expectation of success; and (c) the prior art references teach or suggest all of the claim limitations. In the present case, Applicants submit that the rationale for arriving at an obviousness rejection based upon the cited references or any general knowledge available to the artisan at the time of the invention is lacking.

The Office relies upon Bernard et al. to teach a method of detecting a ligand comprising the step of (a) contacting a sample having a ligand (e.g., $^{125}$I-IgG) with an affinity substrate (PDMS stamp) wherein the affinity substrate comprises an array of receptors that are capable of specifically binding the ligand. The Office further alleges that Bernard et al. teach a step (b) of contacting the affinity substrate with a detection surface (glass or polystyrene) wherein a portion of the ligand that is bound by the receptor is transferred to the detection surface. Bernard et al. fail to teach detection of the ligand on the detection surface by liquid crystal but, instead, utilize radioactive or fluorescent labels attached to the target ligands. No further teaching as to selection of suitable detection surfaces is provided, particularly with respect to guidance in terms of surfaces compatible with both affinity microcontact printing and liquid crystal detection.

In a similar fashion, Renault et al. is relied upon by the Office to teach a method of detecting a ligand (e.g., an antibody) by contacting a ligand-containing sample with an affinity substrate (PDMS stamp), followed by transfer of the ligand to a detection surface, where detection of the ligand is accomplished by fluorescent or gold-labeled antibodies via fluorescence microscopy or atomic force microscopy. Renault et al. fail to teach detection of the ligand via liquid crystal techniques. Like Bernard et al., Renault et al. includes no teaching as to selection of suitable detection surfaces compatible with both affinity

microcontact printing and liquid crystal detection.

The Office relies on Abbott et al. to teach a device having a detection surface to which a ligand may be transferred and its presence subsequently detected by using a liquid crystal. The Office states that one would have been motivated to combine the teachings of Bernard et al. and Abbott et al. or, alternatively, Renault et al. and Abbott et al., because Abbott et al. teach that liquid crystal detection surfaces do not require prelabeling of the ligand and, as such, one would be motivated to stamp the affinity-captured ligand onto the device of Abbott et al. to avoid the need for fluorescent or radioactive labels of the ligands. The Office further states that "one would have a reasonable expectation of success in affinity stamping the surface of Abbott et al. according to the methods of Bernard et al. or Renault et al. because the surface of Abbott et al. is compatible with microcontact printing."

However, neither Bernard et al. nor Renault et al. teach or suggest the use of a detection surface upon which a ligand may be stamped and liquid crystal detection subsequently carried out. Combining affinity microcontact printing with liquid crystal detection is simply not contemplated by these two cited references. The successful detection of affinity stamped ligand on a detection surface by liquid crystal, as opposed to ligand detection by fluorescent or radioactive labeling, is far from a "mere substitution of one known element for another" to obtain predictable results.

While the cited reference to Abbott et al. describes a wide variety of surfaces suitable for liquid crystal detection, the method of detecting affinity microcontact printed ligands via detection surfaces compatible with liquid crystals is not disclosed or suggested by Abbott et al. At most, Abbott et al. recognizes various materials that may be used in the practice of liquid crystal detection and does not show or suggest that detection surfaces may also act to receive a ligand to be detected from an affinity substrate. Reference is now made to column 17 of Abbott et al. where materials and methods are described that can be used to fabricate surfaces ("substrates") on which molecular interactions can be detected using liquid crystals. This section describes various materials that can be used to fabricate surfaces, including inorganic crystals, and glasses and inorganic oxides, metals and organic polymers. In this context, Abbott et al. note that various means can be used to process these materials, including photolithography, photoetching, chemical etching and microcontact printing. However, the transfer of a ligand to be detected by any microcontact printing technique is not described by Abbott et al. Instead, Abbott et al. discuss microcontact printing in the context of forming patterns ("as small as 200 nm") such as, "wells, enclosures, partitions, recesses, inlets, outlets, channels, troughs, diffraction gratings and the like." The discussion of microcontact printing by Abbott et al. is, in fact, in an unrelated context to the transfer of ligand by "affinity" microcontact printing taught by Bernard et al. and Renault et al.

The Office is directed to the Declaration under Rule 1.132 from present inventor Abbott, dated October 9, 2007, in which Dr. Abbott, also an inventor in the cited reference, comments on the above issue and confirms that Abbott et al. did not previously describe microcontact printing as a method to transfer ligand to detection surfaces for subsequent liquid crystal detection. There was not simply indication by Abbott et al. that such a combination of elements/steps would be successful. Accordingly, the Office's contention that the detection surfaces taught by Abbott et al. are compatible with affinity microcontact printing in that the artisan would expect success in ligand detection via liquid crystal methodology is unfounded.

In viewing the combined teachings of the cited references, there is simply no teaching, suggestion, or motivation in the cited references or in the knowledge generally available to the artisan that would have led the artisan to combine the prior art teachings to arrive at the claimed invention. Furthermore, there is no rationale to support a conclusion that one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predicable results to the artisan at the time of the invention. This rationale fails because there was no teaching or suggestion provided by the combined references or the general knowledge available to the artisan at the time of the invention that provided an expectation of success to the artisan, namely, the substitution of liquid crystal detection methods described in Abbott et al. for the fluorescent or radioactive labeling described by Renault et al. and Bernard et al.

For at least the above-stated reasons, the statutory requirements to establish a *prima facie* case of obviousness are clearly lacking from the final Office action. As a result, claim 1 and all claims that depend therefrom are in condition for allowance.

**Conclusion**

Applicants have introduced no new matter in making the above remarks. The Applicants submit that claims 1-6, 10, 11 and 14-23 of the present application recite patentable subject matter deserving of a timely notice of allowance. No additional fees beyond the fees authorized in the accompanying Notice of Appeal are believed due to enter this Pre-Appeal Brief Request for Review; however, if an additional fee(s) is/are required, please charge Deposit Account No. 17-0055 in the amount of the fee.

Respectfully submitted,

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